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     (FILE 'HOME' ENTERED AT 13:58:35 ON 20 SEP 2001)

     FILE 'CAPLUS, EMBASE, MEDLINE, USPATFULL, PCTFULL, EUROPATFULL' ENTERED
     AT 13:59:59 ON 20 SEP 2001
L1           577 SEA ABB=ON  PLU=ON  (TNF OR TUMOR NECRO? FACTOR OR TUMOUR
                 NECRO? FACTOR) AND (HEARING OR COCHLEAR ADJ CELLS OR AUDITORY)

L2           430 SEA ABB=ON  PLU=ON  (TNF OR TUMOR NECRO? FACTOR OR TUMOUR
                 NECRO? FACTOR) AND (HEARING (3A) LOSS OR COCHLEAR (3A)
                 DEGENRAT? OR AUDITORY)
L3           340 SEA ABB=ON  PLU=ON  (TNF OR TUMOR NECRO? FACTOR OR TUMOUR
                 NECRO? FACTOR) (P) (HEARING (3A) LOSS OR COCHLEAR (3A)
                 DEGENRAT? OR AUDITORY)
L4           404 SEA ABB=ON  PLU=ON  (TNF OR TUMOR NECRO? FACTOR OR TUMOUR
                 NECRO? FACTOR) (L) (HEARING (3A) LOSS OR COCHLEAR (3A)
                 DEGENRAT? OR AUDITORY)
L5           406 SEA ABB=ON  PLU=ON  (TNF OR TUMOR NECRO? FACTOR OR TUMOUR
                 NECRO? FACTOR) (L) ((HEARING (3A) LOSS) OR (COCHLEAR (3A)
                 DEGENERAT?) OR AUDITORY)
L6             3 SEA ABB=ON  PLU=ON  (TNF OR TUMOR NECRO? FACTOR OR TUMOUR
                 NECRO? FACTOR) (5A) ((HEARING (3A) LOSS) OR (COCHLEAR (3A)
                 DEGENERAT?) OR AUDITORY)
L7             3 DUP REM L6 (0 DUPLICATES REMOVED)
                 D L7 IBIB KWIC
                 D L7 IBIB KWIC 2-
L8           393 DUP REM L5 (13 DUPLICATES REMOVED)
L9           142 SEA ABB=ON  PLU=ON  (TNF OR TUMOR NECRO? FACTOR OR TUMOUR
                 NECRO? FACTOR) (5A) (INHIBIT? OR MODIF? OR ANTAGONIST OR
                 ANTIBOD?) (P) (HEARING LOSS OR COCHLAR DEGENERAT?)
L10          142 SEA ABB=ON  PLU=ON  (TNF OR TUMOR NECRO? FACTOR OR TUMOUR
                 NECRO? FACTOR) (5A) (INHIBIT? OR MODIF? OR ANTAGONIST OR
                 ANTIBOD?) (P) (HEARING (3A) LOSS OR COCHLEAR (3A) DEGENERAT?)
                 D L10 1-5 IBIB KWIC
                 D L10 130-142 IBIB KWIC
L12          127 SEA ABB=ON  PLU=ON  L10 (P) (INTERLEUKIN-1 OR IL-1)
                 D L12 120-127 IBIB KWIC
```

10 ANSWER 139 OF 142 PCTFULL COPYRIGHT 2001 MicroPatent

ACCESSION NUMBER: 1997042966 PCTFULL

TITLE (ENGLISH): THERAPEUTIC USES OF BPI PROTEIN PRODUCTS FOR HUMAN MENINGOCOCCEMIA

TITLE (FRENCH): APPLICATIONS THERAPEUTIQUES DE PRODUITS PROTEIQUES BACTERICIDES/AUGMENTANT LA PERMEABILITE (BPI) DANS LE CAS DE MENINGOCOCCEMIES CHEZ L'HOMME

INVENTOR(S): GIROIR, Brett, P.; SCANNON, Patrick, J.

PATENT ASSIGNEE(S): XOMA CORPORATION

LANGUAGE OF PUBL.: English

LANGUAGE OF FILING: English

DOCUMENT TYPE: Patent

PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9742966	A1	19971120

DESIGNATED STATES: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN GH KE LS MW SD SZ UG AM AZ BY KG KZ MD RU TJ TM AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

APPLICATION INFO.: WO 1997-US8016 19970509

PRIORITY (ORIGINAL): US 1996-08/644287 19960510

DETD . . . culture or immunologic assays. Systemic hemodynarnic signs, severe coagulopathy and intravascular thrombosis are notably absent. If properly treated, mortality is rare and neurologic sequelae, including sensineural **hearing loss**, is uncommon. The approach to diagnosis and treatment of meningococcal meningitis is the same as with other forms of bacterial meningitis.

. . .

et al., Blood 85:3437-3443 (1995); de Winter et at., J. Inflam. 45:193-206 (1995)]. Thornton et al., FASEB J., 8(4):AI37, 1994, report that BPI **inhibited** the release of **TNF** in itro by human inflammatory cells in response to LOS derived from two Neisseria species, N.

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L12 ANSWER 125 OF 127 PCTFULL COPYRIGHT 2001 MicroPatent
ACCESSION NUMBER: 1993006865 PCTFULL
TITLE (ENGLISH): TREATMENT OF OCULAR INFLAMMATION BY BLOCKAGE OF CELL ADHESION MOLECULES
TITLE (FRENCH): TRAITEMENT DE L'INFLAMMATION OCULAIRE PAR BLOCAGE DES MOLECULES D'ADHESION CELLULAIRE
INVENTOR(S): WHITCUP, Scott, M.; CHAN, Chi-Chao; NUSSENBLATT, Robert, B.
PATENT ASSIGNEE(S): THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT
LANGUAGE OF PUBL.: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9306865	A1	19930415

DESIGNATED STATES: AU CA JP AT BE CH DE DK ES FR GB GR IE IT LU MC NL SE

APPLICATION INFO.:	WO 1992-US8556	19921002
PRIORITY (ORIGINAL):	US 1991-770026	19911004
	US 1992-822042	19920117

DETD Case 2 A 72-year-old black woman with a 30-year history of bilateral recurrent panuveitis with exudative retinal detachments, apapilledema, **hearing loss**, and vitiligo was diagnosed with Vogt-Koyanagi-Harada syndrome (Chan, C-C. et al., Am. J.

. . .

six uveitic eyes showed mild staining for TNF-B (cases 1, 2, 3 and 6), and two uveitic eyes showed no staining with **antibody** against **TNF**-B. None of the control eyes stained positively for either TNF-a and TNF-B.

. . .

the regulation of adhesion molecule expression. The secretions of cytokines, particularly by the infiltrating T lymphocytes, probably plays an important regulatory function. Gamma-interferon, **interleukin-1**, and tumor necrosis factor cause the strong induction of ICAM-1, although different cells vary as to which cytokines will i

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L12 ANSWER 122 OF 127 PCTFULL COPYRIGHT 2001 MicroPatent
ACCESSION NUMBER: 1999053927 PCTFULL
TITLE (ENGLISH): METHODS FOR TREATING AND PREVENTING INSULIN RESISTANCE AND
RELATED DISORDERS
TITLE (FRENCH): PROCEDES POUR TRAITER ET PREVENIR LA RESISTANCE A L'INSULINE ET
LES TROUBLES QUI Y SONT LIES
INVENTOR(S): GREENBERG, Andrew, S.
PATENT ASSIGNEE(S): TRUSTEES OF TUFTS COLLEGE
LANGUAGE OF PUBL.: English
LANGUAGE OF FILING: English
DOCUMENT TYPE: Patent
PATENT INFORMATION:

NUMBER	KIND	DATE
WO 9953927	A1	19991028

DESIGNATED STATES: JP US AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
APPLICATION INFO.: WO 1999-US8364 19990416
PRIORITY (ORIGINAL): US 1998-60/082152 19980417
US 1998- 19980423

DETD . . . years while attacking the blood
vessels and nerves,
Diabetics, as a group, are far more often afflicted with blindness,
heart disease, stroke, kidney
disease, **hearing loss**, gangrene and impotence. One
third of all visits
to physicians are
occasioned by this disease and its complications, and diabetes and its
complications. . .
. . .
activity of JNK and also, but to a
lesser extent, the activity
of ERKI" kinase. Furthermore, a prostaglandin derivative was also shown
to **inhibit TNF**-
u induced lipolysis and to **inhibit** ERKI/2 and YNK-1 activation.
Furthermore, as shown
herein, an inhibitor of a ERK/MA-P kinase decreases TNF-a induced
lipolysis. In addition,
contrary to JNK and. . .) 8 pathway
stimulates TNF-a
induced lipolysis. Thus, the Examples described herein indicate that
inhibition of the JNK
pathway and the ERK/MAP kinase pathway **inhibit TNF**-(y
induced lipolysis,
whereas
inhibition of the p3) 8 pathway increases TNF-a induced
lipolysis.

3. Compounds which **inhibit TNF**-a induced lipolysis
The invention provides methods for inhibitino, or blocking lipolysis of
adipocytes. In
In
a preferred embodiment, lipolysis is TNF-a induced lipolysis. In. . .
. . .
kinases
(SAPKs), are
members of the mitogen-activated protein (MAP) kinase group which are
activated in
response to cytokines, such as TNF, e.g., TNF-(x and **IL-1**, and exposure
to environmental
ZD
stress, including ultraviolet light, heat shock, and osmotic stress (U.S.
Pat. No. 5605808; B.

Other compounds of the invention
Other preferred compounds of the invention include compounds which **inhibit TNF**-a.

Such compounds include those which inhibit the production of TNTF-a, as well as those which
specifically inhibit its activity, e.g., by interfering. . . its interaction With a receptor. For
example, an inhibitor can be an antibody binding specifically to, and inhibiting the activity of
TNTF-a. Yet other **inhibitory** compounds include **inhibitors** of a **TNF**-a
receptor or of a
molecule interacting therewith, such as the NLADD protein (Schievella et a]. (1997) J Biol,
Chein. 272:12069). Thus, within the scope of the invention are antisense and triplex
molecules; which specifically **inhibit** the expression of **TNF**-a, a TNF-u.
receptor, or molecule
interactina with TNF-u, or' uch as MADD.

. . .
thereof As described in the Examples,
NaSal has in fact
been shown herein to inhibit JNK activation by TNTF-u. in adipocytes and to **inhibit TNF**-cz
induced lipolysis in adlpoc tes. NaSal has also been described as being capable of **inhibiting**
TNF-Induced activation of JNK and p42/p44 MAP kinases in FS4 fibroblasts
(Schwenger et
al. (1997) P.N.A.S. tWA 94:2869) and Schwenger et al. (1996). . .

. . .
discovery that the.TNK
and the EPK/MAP
kinase pathways are involved in TNF-a induced lipolysis, and that iri-
hibition of these kinase
pathways decreases or **inhibits TNF**-a induced
lipolysis. It has also been
shown that PPAR-y
agonists inhibit TNIF-a induced lipolysis. Thus, the invention pertains to any disease or d1sorder
which. . .

In a particular embodiment, insulin resistance or other disease or condition associated
with an abnormal FFA level is reduced, eliminated or **inhibited**, by
blocking **TNF**-a action, e-,(_,-
by neutralizing TNF-u, in the serum (Le., circulating T'NT,-ct) or in the adipose tissue.

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methods of the invention comprise
determining the
activity of a PPAR-y receptor, In fact, since binding of a ligand to a PPAR-y receptor **inhibits**
TNF-a induced lipolysis, a defective PPAR-y may result in increased TNF-
a induced lipolysis.

. . .
of detection is by performing ELISA assays. An ELISA assay for the detection of
human T.NF-rt, as well as the production of **antibodies** against human **TNF**-
U., is described, e.g.,
in U.S. Patent No. 5,71.6,972 by Adams eL a]. Antibodies for performing

these assays are also
commercially available, such as. . .
. . .
showli in Figure 1. These indicate that lipolysis in the
adipocy-tes induced
by 2 ng/ml (Panel A) or 20 ng/ml (Panel B) **TNF**-a is
significantly
inhibited by the addition of
2 or 20 mM NaSal. In fact, NaSal inhibited glycerol production by 3T3)-
LI adipoc tes induced
by. . .

Example 2: NaSal **inhibits** **TNF**-a induced JNK-1
activation in adipocytes
This example shows that NaSal inhibits JNTK-1 activation by TNLF-a in
adipocvtes.

Thus, since NaSal **inhibits** **TNF**-a induced lipolysis
and NaSal
significantly reduces JN-K-
I activation, JNK-I activation is likely to play a significant role in
blocking lipolysis induced by
TNTF-u.

Example 3. NaSal partially **inhibits** **TNF**-ct induced
NMP kinase
activation
This example shows that, whereas JNK- I activation by **TNF**-u is
significantly **inhibited**
by NaSal, activation of NIALP kinases by TNF-a is not significantly
inihbited by NaSal.

Examplt-4- NUP kinase **inhibitor** PD98059 decreases **TNF**
-a induced
lipolysis
This Example demonstrates that inhibition of ERKI/2 by PD98059 decreases
TNTF-a
induced lipolysis.

Example 5: **Inhibition** of-p38 kinase stimulates **TNF**-u
induced lipolysis
This example shows; that, contrarily to JNK and ERK 1/22 signal pathways,
inhibition of
the p38 sional pathway stimulates TN-.-F-a induced. . .
. . .
ERK 1/2 kinase activity, BRL
does not significantly aft-'ect
the activity of JNK- I and ERK 1/2 kinases. Thus, BRL does not
inhibit
TNF-a induced lipolysis
by decreasing the activity of JNK- I and "K/ERK.

Example 7: PGJ2 **inhibits** **TNF**-u induced activation of
JNK-I and ERK1/2
This example shows that TNF-rt induced activation of JNIK-1 and ERKI/2-
can be
inhibited by PGJ2.
. . .
p3 8. Total protein I s
shown in Figure 7 panel
B. Furthermore, Figure 7 panels C and D shows that PGJ2 significantly
inhibits the **TNF**-cz
induced 'increase in ERK 1 /2 and that of JNK- I kinase activity. Thus.,
PGJ2, which is an agonist
of the PPAR-y receptor may function in a similar manner to NaSal to
inhibit **TNF**-a induced
lipolysis, i.e., by modulating TVAP kinases, e.g., ERKI/2 and JNK-I.

Example 8: **Inhibition** of JNK-1 decreases **TNF**-u,
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This example demonstrates an experiment that a person of skill in the
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DETD . . . years while attacking the blood vessels and nerves, Diabetics, as a group, are far more often afflicted with blindness, heart disease, stroke, kidney disease, **hearing loss**, gangrene and impotence. One third of all visits to physicians are occasioned by this disease and its complications, and diabetes and its complications. . .

. . . activity of JNK and also, but to a lesser extent, the activity of ERKI" kinase. Furthermore, a prostaglandin derivative was also shown to **inhibit TNF**-u induced lipolysis and to **inhibit** ERKI/2 and YNK-1 activation. Furthermore, as shown herein, an inhibitor of a ERK/MA-P kinase decreases TNF-a induced lipolysis. In addition, contrary to JNK and. . .) 8 pathway stimulates TNF-a induced lipolysis. Thus, the Examples described herein indicate that inhibition of the JNK pathway and the ERK/MAP kinase pathway **inhibit TNF**-(y induced lipolysis, whereas **inhibition** of the p3) 8 pathway increases TNF-a induced lipolysis.

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HEARING.DWPI,EPAB,JPAB,USPT,PGPB.	21362
HEARINGS.DWPI,EPAB,JPAB,USPT,PGPB.	233
LOSS.DWPI,EPAB,JPAB,USPT,PGPB.	655519
LOSSES.DWPI,EPAB,JPAB,USPT,PGPB.	164374
(MENINGITIS SAME (HEARING ADJ LOSS)).USPT,PGPB,JPAB,EPAB,DWPI.	16

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MENINGITI.DWPI,EPAB,JPAB,USPT,PGPB.	5
HEARING.DWPI,EPAB,JPAB,USPT,PGPB.	21362
HEARINGS.DWPI,EPAB,JPAB,USPT,PGPB.	233
LOSS.DWPI,EPAB,JPAB,USPT,PGPB.	655519
LOSSES.DWPI,EPAB,JPAB,USPT,PGPB.	164374
(MENINGITIS SAME (HEARING ADJ LOSS)).USPT,PGPB,JPAB,EPAB,DWPI.	16

Database: US Patents Full-Text Database; US Pre-Grant Publication Full-Text Database; JPO Abstracts Database; EPO Abstracts Database; Derwent World Patents Index; IBM Technical Disclosure Bulletins

Refine Search: meningitis same (hearing adj loss) Clear

Search History

Today's Date: 9/20/2001

DB Name	Query	Hit Count	Set Name
USPT,PGPB,JPAB,EPAB,DWPI	meningitis same (hearing adj loss)	16	L6
USPT,PGPB,JPAB,EPAB,DWPI	meningitis adj5 (hearing adj loss)	1	L5
USPT,PGPB,JPAB,EPAB,DWPI	meningitis adj5(hearing adj loss)	1	L4
USPT,PGPB,JPAB,EPAB,DWPI	(TNF or tumor adj necro$3 adj factor or tumour adj necro$4 adj factor) same (il-1 or interleukin-1) and (hearing adj loss or cochlear adj degenrat$)	13	L3
USPT,PGPB,JPAB,EPAB,DWPI	(TNF or tumor adj necro$3 adj factor or tumour adj necro$4 adj factor) same meningitis and (hearing adj loss or cochlear adj degenrat$)	4	L2
USPT,PGPB,JPAB,EPAB,DWPI	(TNF or tumor adj necro$3 adj factor or tumour adj necro$4 adj factor) same (hearing adj loss or cochlear adj degenrat$)	4	L1

DB Name	Query	Hit Count	Set Name
USPT,PGPB,JPAB,EPAB,DWPI	meningitis same (hearing adj loss)	16	L6
USPT,PGPB,JPAB,EPAB,DWPI	meningitis adj5 (hearing adj loss)	1	L5
USPT,PGPB,JPAB,EPAB,DWPI	meningitis adj5(hearing adj loss)	1	L4
USPT,PGPB,JPAB,EPAB,DWPI	(TNF or tumor adj necro$3 adj factor or tumour adj necro$4 adj factor) same (il-1 or interleukin-1) and (hearing adj loss or cochlear adj degenrat$)	13	L3
USPT,PGPB,JPAB,EPAB,DWPI	(TNF or tumor adj necro$3 adj factor or tumour adj necro$4 adj factor) same meningitis and (hearing adj loss or cochlear adj degenrat$)	4	L2
USPT,PGPB,JPAB,EPAB,DWPI	(TNF or tumor adj necro$3 adj factor or tumour adj necro$4 adj factor) same (hearing adj loss or cochlear adj degenrat$)	4	L1